

WO9948530

Title:
**COMBINATION THERAPY FOR THE TREATMENT OF BENIGN PROSTATIC
HYPERPLASIA**

Abstract:

This invention relates to combination therapy for the treatment of benign prostatic hyperplasia comprising an alpha-1a antagonist and an endothelin antagonist. More specifically, the use of a selective alpha-1a adrenergic receptor antagonist in combination with a subtype non-selective endothelin antagonist provides relief of lower urinary tract symptoms in patients with symptomatic prostatism or benign prostatic hyperplasia. This combination therapy improves lower urinary tract symptoms including increasing urine flow rate, decreasing residual urine volume and improving overall obstructive and irritative symptoms in patients with benign prostatic hyperplasia or symptomatic prostatism.



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(54) Title: COMBINATION THERAPY FOR THE TREATMENT OF BENIGN PROSTATIC HYPERPLASIA			
(57) Abstract			
<p>This invention relates to combination therapy for the treatment of benign prostatic hyperplasia comprising an alpha-1a antagonist and an endothelin antagonist. More specifically, the use of a selective alpha-1a adrenergic receptor antagonist in combination with a subtype non-selective endothelin antagonist provides relief of lower urinary tract symptoms in patients with symptomatic prostatism or benign prostatic hyperplasia. This combination therapy improves lower urinary tract symptoms including increasing urine flow rate, decreasing residual urine volume and improving overall obstructive and irritative symptoms in patients with benign prostatic hyperplasia or symptomatic prostatism.</p>			

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TITLE OF THE INVENTION
COMBINATION THERAPY FOR THE TREATMENT OF BENIGN
PROSTATIC HYPERPLASIA

5 FIELD OF THE INVENTION

The present invention provides combination therapy for the treatment of benign prostatic hyperplasia. More particularly, the combination comprises an alpha-1a adrenergic receptor antagonist with an endothelin antagonist, and optionally a 5a-reductase inhibitor, for relief of lower urinary tract symptoms in patients with symptomatic prostatism or benign prostatic hyperplasia.

BACKGROUND OF THE INVENTION

Benign prostatic hyperplasia, also known as benign prostatic hypertrophy or BPH, is an illness typically affecting men over fifty years of age, increasing in severity with increasing age. The symptoms of the condition include, but are not limited to, increased difficulty in urination and sexual dysfunction. These symptoms are induced by enlargement, or hyperplasia, of the prostate gland. As the prostate increases in size, it impinges on free-flow of fluids through the male urethra. Concomitantly, the increased noradrenergic innervation of the enlarged prostate leads to an increased adrenergic tone of the bladder neck and urethra, further restricting the flow of urine through the urethra.

Bladder outlet obstruction (BOO) in BPH patients results from a static component of increased prostatic mass which physically impinges on the urethra and a dynamic component of increased contractile tone of the prostatic-urethral smooth muscle. Standard treatment of BPH involves surgical or pharmacological intervention. Surgical intervention, either by removal of the prostate via radical prostatectomy or removing the prostatic adenoma via transurethral resection of the prostate alleviates both the static and dynamic components of BOO since the entire prostate or the majority of the prostatic smooth muscle is removed. Although these procedures result in the most marked improvement in symptoms, there is the possibility of

mortality and morbidity since these are invasive surgical procedures. Many patients suffer incontinence and retrograde ejaculation as a consequence of these surgical procedures. Because of the chances for morbidity and mortality, these procedures are not optimum for patients with mild to moderate symptoms in a disease which is not life-threatening.

Pharmacological treatment with 5 α -reductase inhibitors such as finasteride reduces the size of the prostate, thereby alleviating the static component of BOO. However, the symptomatic improvement following this therapy is significantly less than that following surgery. The lesser efficacy is likely mechanism-based in that 5 α -reductase inhibitors decrease the size of the prostate by reducing the amount of epithelial tissue without affecting the smooth muscle, therefore the dynamic component of BOO may still be present.

Another pharmacological therapy involves the administration of subtype nonselective α -1 adrenergic receptor antagonists. These agents relax the prostatic-urethral smooth muscle by blocking endogenous sympathetic tone hence affecting the dynamic component of BOO. However, these agents were originally developed to treat hypertension and have effects on the cardiovascular system which include decreasing blood pressure and causing orthostatic hypotension. The efficacy of this therapy is also significantly less than that following surgery. Efficacy of these agents may be limited by dose-related cardiovascular side-effects, the remaining static component of BOO, and/or because another endogenous substance contributes to the dynamic prostatic-urethral tone.

The predominant α -1 adrenergic receptor subtype responsible for α 1 agonist mediated contraction of human prostatic-urethral smooth muscle is the α -1a subtype. Animal studies suggest that the α -1a receptor is not involved in normal blood pressure regulation, therefore selective α -1a receptor antagonists may not have the dose-limiting side-effects of subtype nonselective antagonists. The only other substances identified to potentially contract human prostate tissue are endothelins (ET) via both the ET-A and ET-B receptors. Endothelin-1 is found in very high concentrations in the

prostate and appears to be produced locally in the epithelial tissue in the prostate (Langenstroer, et al 1993 J. of Urology 149:495-99). Alpha adrenergic tone is known to be involved in the dynamic component of BPH based on the efficacy of the subtype nonselective compounds approved for clinical use. The role of ET in BPH is unknown at this time.

It is therefore an object of the invention to find an improved therapy for treating benign prostatic hyperplasia. It is a further object of the invention to find improved methods for relaxing lower urinary tract tissue in patients in need of such treatment. Still a further object of the present invention is to improve lower urinary tract symptoms which include increasing urine flow rate, decreasing residual urine volume and improving overall obstructive and irritative symptoms in patients with benign prostatic hyperplasia or symptomatic prostatism.

It has now been found that combination therapy with an alpha-1a antagonist and an endothelin antagonist, preferably a mixed ET-A/ET-B antagonist, is useful for treating benign prostatic hyperplasia, for relaxing lower urinary tract tissue, and for improving lower urinary tract symptoms which include increasing urine flow rate, decreasing residual urine volume and improving overall obstructive and irritative symptoms in patients with benign prostatic hyperplasia or symptomatic prostatism. The advantage of the combined administration of an alpha-1a antagonist and an ET-A/ET-B antagonist is that two putative components which determine the dynamic prostatic tone would be inhibited without the dose-limiting side-effects observed with subtype non selective alpha-1 antagonists.

SUMMARY OF THE INVENTION

The present invention provides a composition comprising an alpha-1a adrenergic receptor antagonist and an endothelin antagonist, and pharmaceutically acceptable salts thereof.

In one embodiment of the instant invention is the composition of an alpha-1a adrenergic receptor antagonist and an endothelin antagonist wherein the alpha-1a adrenergic receptor

antagonist is a selective alpha-1a adrenergic receptor antagonist; and the pharmaceutically acceptable salts thereof.

5 In a class of the embodiment is the composition comprising a selective alpha-1a adrenergic receptor antagonist and an endothelin antagonist wherein the selective alpha-1a adrenergic receptor antagonist is selected from Compound A, Compound C, Compound D, Compound E, KMD-3213, tamsulosin, REC 15/2739 or A131701; and the pharmaceutically acceptable salts thereof.

10 In a subclass of the embodiment is the composition mentioned above wherein the selective alpha-1a adrenergic receptor antagonist is Compound A.

In another subclass of the embodiment is the composition mentioned above wherein the selective alpha-1a adrenergic receptor antagonist is Compound C.

15 In another subclass of the embodiment is the composition mentioned above wherein the selective alpha-1a adrenergic receptor antagonist is Compound D.

In another subclass of the embodiment is the composition mentioned above wherein the selective alpha-1a adrenergic receptor antagonist is Compound E.

20 In a second class of the embodiment is the composition comprising an alpha-1a adrenergic receptor antagonist and an endothelin antagonist wherein the endothelin antagonist is a subtype non-selective endothelin antagonist; and the pharmaceutically acceptable salts.

25 In a subclass of the second class of the embodiment is the composition wherein the subtype non-selective endothelin antagonist is selected from Compound B, bosentan, SB217242, SB209670, A 127722 or A 182086.

30 Illustrating the subclass is the composition wherein the subtype non-selective endothelin antagonist is Compound B.

35 Illustrating the embodiment is the composition comprising a selective alpha-1a adrenergic receptor antagonist and an endothelin antagonist wherein the selective alpha-1a adrenergic receptor antagonist is Compound A, Compound D, Compound E, or a

pharmaceutically acceptable salt thereof; and the endothelin antagonist is Compound B or a pharmaceutically acceptable salt thereof.

15 Illustrating the embodiment is the composition comprising a selective alpha-1a adrenergic receptor antagonist and an endothelin antagonist wherein the selective alpha-1a adrenergic receptor antagonist is Compound A and the endothelin antagonist is Compound B; and pharmaceutically acceptable salts thereof.

Also illustrating the embodiment is the composition comprising a selective alpha-1a adrenergic receptor antagonist and an
20 endothelin antagonist wherein the selective alpha-1a adrenergic receptor antagonist is Compound D and the endothelin antagonist is Compound B; and pharmaceutically acceptable salts thereof.

Also illustrating the embodiment is the composition comprising a selective alpha-1a adrenergic receptor antagonist and an
15 endothelin antagonist wherein the selective alpha-1a adrenergic receptor antagonist is Compound E and the endothelin antagonist is Compound B; and pharmaceutically acceptable salts thereof.

Further illustrating the embodiment is the composition comprising an alpha-1a adrenergic receptor antagonist, an endothelin
20 antagonist, a 5a-reductase inhibitor, and pharmaceutically acceptable salts thereof.

A second embodiment of the invention is a method of treating benign prostatic hyperplasia in a subject in need thereof which comprises administering to the subject an effective amount of an alpha-
25 1a antagonist, an endothelin antagonist, and optionally a 5a-reductase inhibitor.

A class of the second embodiment is the method wherein the alpha-1a adrenergic receptor antagonist is selected from Compound A, Compound D, Compound E, KMD-3213, tamsulosin, REC 15/2739,
30 A131701, or pharmaceutically acceptable salts thereof; and the endothelin antagonist is selected from Compound B, bosentan, SB217242, SB209670, A 127722, A 182086, or pharmaceutically acceptable salts thereof.

A subclass of the second embodiment is the method wherein
35 the alpha-1a adrenergic receptor antagonist is Compound D or a

pharmaceutically acceptable salt thereof, and the endothelin antagonist is Compound B or a pharmaceutically acceptable salt thereof.

- Another subclass of the second embodiment is the method wherein the alpha-1a adrenergic receptor antagonist is Compound E or a pharmaceutically acceptable salt thereof, and the endothelin antagonist is Compound B or a pharmaceutically acceptable salt thereof.

- Another class of the second embodiment is the method wherein the alpha-1a adrenergic receptor antagonist is selected from Compound A, Compound C, KMD-3213, tamsulosin, REC 15/2739 or A131701 and the endothelin antagonist is selected from Compound B, bosentan, SB217242, SB209670, A 127722 or A 182086.

A subclass of the second embodiment is the method wherein the alpha-1a adrenergic receptor antagonist is Compound A and the endothelin antagonist is Compound B.

- Another subclass of the second embodiment is the method wherein the alpha-1a adrenergic receptor antagonist is Compound C and the endothelin antagonist is Compound B.

- A third embodiment of the instant invention is a method of relaxing lower urinary tract tissue in a subject in need thereof which comprises administering to the subject an effective amount of an alpha-1a antagonist, an endothelin antagonist, and optionally a 5a-reductase inhibitor.

- A class of the third embodiment is the method wherein the alpha-1a adrenergic receptor antagonist is selected from Compound A, Compound D, Compound E, KMD-3213, tamsulosin, REC 15/2739, A131701, or pharmaceutically acceptable salts thereof; and the endothelin antagonist is selected from Compound B, bosentan, SB217242, SB209670, A 127722, A 182086, or pharmaceutically acceptable salts thereof.

- A subclass of the third embodiment is the method wherein the alpha-1a adrenergic receptor antagonist is Compound D or a pharmaceutically acceptable salt thereof, and the endothelin antagonist is Compound B or a pharmaceutically acceptable salt thereof.

- Another subclass of the third embodiment is the method wherein the alpha-1a adrenergic receptor antagonist is Compound E or

a pharmaceutically acceptable salt thereof, and the endothelin antagonist is Compound B or a pharmaceutically acceptable salt thereof.

Another class of the third embodiment is the method wherein the alpha-1a adrenergic receptor antagonist is selected from Compound A, Compound C, KMD-3213, tamsulosin, REC 15/2739 or A131701 and the endothelin antagonist is selected from Compound B, bosentan, SB217242, SB209670, A 127722 or A 182086.

A subclass of the third embodiment is the method wherein the alpha-1a adrenergic receptor antagonist is Compound A and the endothelin antagonist is Compound B.

In another subclass of the third embodiment is the method wherein the alpha-1a adrenergic receptor antagonist is Compound C and the endothelin antagonist is Compound B.

A fourth embodiment of the invention is a method of improving lower urinary tract symptoms in a benign prostatic hyperplasia patient which comprises administering to the subject an effective amount of an alpha-1a antagonist, an endothelin antagonist, and optionally a 5a-reductase inhibitor.

A class of the fourth embodiment is method for increasing urine flow rate.

A second class of the fourth embodiment is the method for decreasing residual urine volume.

A third class of the fourth embodiment is a method of improving lower urinary tract symptoms in a benign prostatic hyperplasia patient which comprises administering to the subject an effective amount of an alpha-1a antagonist, an endothelin antagonist, and optionally a 5a-reductase inhibitor wherein the alpha-1a adrenergic receptor antagonist is selected from Compound A, Compound C, KMD-3213, tamsulosin, REC 15/2739 or A131701 and the endothelin antagonist is selected from Compound B, bosentan, SB217242, SB209670, A 127722 or A 182086.

A fourth class of the fourth embodiment is a method of improving lower urinary tract symptoms in a benign prostatic hyperplasia patient which comprises administering to the subject an effective amount of an alpha-1a antagonist, an endothelin antagonist,

- and optionally a 5a-reductase inhibitor wherein the alpha-1a adrenergic receptor antagonist is selected from Compound A, Compound D, Compound E, KMD-3213, tamsulosin, REC 15/2739, A131701, or pharmaceutically acceptable salts thereof; and the endothelin antagonist is selected from Compound B, bosentan, SB217242, SB209670, A 127722, A 182086, or pharmaceutically acceptable salts thereof.

A subclass of the fourth embodiment is the method wherein the alpha-1a adrenergic receptor antagonist is Compound A and the endothelin antagonist is Compound B.

- Another subclass of the fourth embodiment is the method wherein the alpha-1a adrenergic receptor antagonist is Compound C and the endothelin antagonist is Compound B.

- Still another subclass of the fourth embodiment is the method wherein the alpha-1a adrenergic receptor antagonist is Compound D or a pharmaceutically acceptable salt thereof, and the endothelin antagonist is Compound B or a pharmaceutically acceptable salt thereof.

- Still another subclass of the fourth embodiment is the method wherein the alpha-1a adrenergic receptor antagonist is Compound E or a pharmaceutically acceptable salt thereof, and the endothelin antagonist is Compound B or a pharmaceutically acceptable salt thereof.

- A fifth embodiment of the invention is a pharmaceutical composition comprising an alpha-1a adrenergic receptor antagonist and an endothelin antagonist, and pharmaceutically acceptable salts thereof, and a pharmaceutically acceptable carrier.

- A class of the fifth embodiment is a pharmaceutical composition comprising an alpha-1a adrenergic receptor antagonist and an endothelin antagonist, wherein the alpha-1a adrenergic receptor antagonist is Compound A and the endothelin antagonist is Compound B, and pharmaceutically acceptable salts thereof, and a pharmaceutically acceptable carrier.

- Another class of the fifth embodiment is a pharmaceutical composition comprising an alpha-1a adrenergic receptor antagonist and an endothelin antagonist, wherein the alpha-1a adrenergic receptor

antagonist is Compound C and the endothelin antagonist is Compound B, and pharmaceutically acceptable salts thereof, and a pharmaceutically acceptable carrier.

- 5 Another class of the fifth embodiment is a pharmaceutical composition comprising an alpha-1a adrenergic receptor antagonist and an endothelin antagonist, wherein the alpha-1a adrenergic receptor antagonist is Compound D and the endothelin antagonist is Compound B, and pharmaceutically acceptable salts thereof, and a pharmaceutically acceptable carrier.

- 10 Another class of the fifth embodiment is a pharmaceutical composition comprising an alpha-1a adrenergic receptor antagonist and an endothelin antagonist, wherein the alpha-1a adrenergic receptor antagonist is Compound E and the endothelin antagonist is Compound B, and pharmaceutically acceptable salts thereof, and a pharmaceutically acceptable carrier.

15 Exemplifying the invention is a pharmaceutical composition made by combining an alpha-1a antagonist, an endothelin antagonist, and pharmaceutically acceptable salts thereof, and a pharmaceutically acceptable carrier.

- 20 Further exemplifying the invention is a process for making a pharmaceutical composition comprising combining an alpha-1a antagonist, an endothelin antagonist, and pharmaceutically acceptable salts thereof, and a pharmaceutically acceptable carrier.

25 DETAILED DESCRIPTION OF THE INVENTION

- This invention relates to combination therapy for the treatment of benign prostatic hyperplasia comprising an alpha-1a antagonist and an endothelin antagonist. More specifically, the use of a selective alpha-1a adrenergic receptor antagonist in combination with a subtype non-selective endothelin antagonist, and optionally a 5a-reductase inhibitor (e.g., finasteride), provides relief of lower urinary tract symptoms in patients with symptomatic prostatism or benign prostatic hyperplasia.. This combination therapy improves lower urinary tract symptoms including increasing urine flow rate,

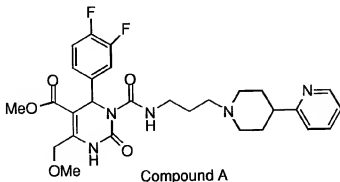
decreasing residual urine volume and improving overall obstructive and irritative symptoms in patients with benign prostatic hyperplasia or symptomatic prostatism. The combinations of the present invention result in improvement of symptoms associated with BPH by blocking endogenous noradrenergic and endothelin-mediated smooth muscle contraction of the smooth muscle in the lower urinary tract including the prostate, urethra, bladder neck and detrusor to reduce bladder outlet obstruction, improve bladder compliance, and/or decrease detrusor instability.

For use in medicine, the salts of the compounds of this invention refer to non-toxic "pharmaceutically acceptable salts." Other salts may, however, be useful in the preparation of the compounds according to the invention or of their pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulphuric acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid.

The instant invention includes the combination wherein all of the individual components are in the form of pharmaceutically acceptable salts and the combination wherein one or more of the individual components is in the form of a pharmaceutically acceptable salt while other of the components are used as the free base.

Recently, a number of alpha-1a adrenergic receptor antagonist compounds have been disclosed as being useful in the treatment of BPH. These alpha-1a adrenergic receptor antagonists and their utility in treating BPH and inhibiting contraction of lower urinary tract tissue are described in PCT International Application Publication No. WO 96/14846, published 23 May 1996. More particularly, the compound (+)-5-Methoxycarbonyl-6-(3,4-difluorophenyl)-4-methoxymethyl-1-[N-{3-(4-(2-pyridyl)piperidin-1-yl)propyl}-carboxamido-2-oxo-1,2,3,6-tetrahydropyrimidine, disclosed in Example 30 of WO 96/14846, and referred to herein as "Compound A," is a potent and

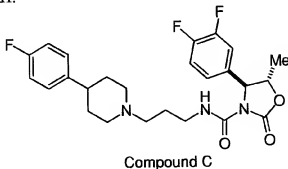
selective antagonist of the alpha-1a adrenergic receptor antagonist and is useful in the treatment of BPH.



- Compound A is prepared according to the procedure of Example 30 in WO 96/14846 or according to the processes disclosed in detail herein. The identification of Compound A as an alpha-1a adrenergic receptor antagonist was established according to the assays described in WO 96/14846.

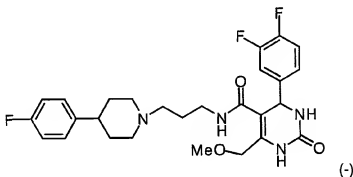
- Compound A, and pharmaceutically acceptable salts thereof exhibit high selectivity for the human alpha-1a adrenergic receptor. One implication of this selectivity is that these compounds display selectivity for lowering intraurethral pressure without substantially affecting diastolic blood pressure.

- The term "Compound C" as used herein is *trans*(+)-4-(3,4-difluorophenyl)-5-methyl-2-oxo-oxazolidine-3-carboxylic acid {3-[4-(4-fluorophenyl)-piperidin-1-yl]propyl}amide, a potent and selective antagonist of the alpha-1a adrenergic receptor antagonist useful in the treatment of BPH.



Compound C is prepared according to the procedures described herein.

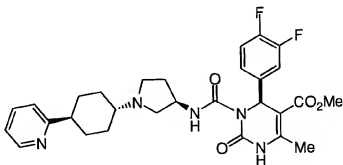
- 5 The term "Compound D" as used herein is (-)-4-(3,4-difluorophenyl)-6-methoxymethyl-2-oxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid {3-[4-(4-fluorophenyl)-piperidin-1-yl]-propyl}-amide. Compound D is a potent and selective antagonist of the alpha-1a adrenergic receptor antagonist useful in the treatment of BPH.



Compound D

Compound D can be prepared as described below.

- 10 The term "Compound E" as used herein is (4S)-trans-4-(3,4-difluorophenyl)-3-[1-(4-pyridin-2-yl-cyclohexyl)-(3R)-pyrrolidin-3-ylcarbamoyl]-6-methyl-2-oxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid methyl ester.



Compound E

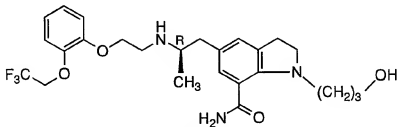
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Compound E is a potent and selective antagonist of the alpha-1a adrenergic receptor antagonist useful in the treatment of BPH.

Compound E is disclosed in WO 98/57641 and can be prepared in accordance with the procedure of Example 48 in WO 98/57641.

KMD-3213 is 1-(3-Hydroxypropyl)-5-[2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethylamino]propyl]indoline-7-carboxamide.

5



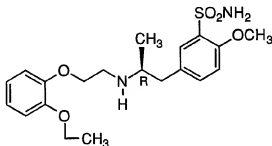
KMD 3213

KMD-3213 is useful in the treatment of dysuria and can be prepared according to the procedures contained in U.S. Patent No. 5,387,603 which issued on February 7, 1995.

10

Tamsulosin is (R)-5-[2-[[2-(2-Ethoxyphenoxy)ethyl]amino]propyl]-2-methoxybenzenesulfonamide monohydrochloride, also known as tamsulosin hydrochloride, LY253351, R-(-)-YM-12617, YM-12617-1, YM617, and FLOMAX®.

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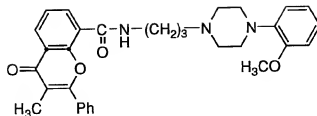


Tamsulosin

Tamsulosin is an alpha 1-a adrenergic receptor antagonist and can be prepared according to the procedures outlined in U.S. Patent No. 4,703,063.

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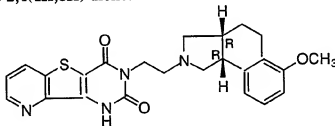
REC 15/2739 is N-[3-[4-(2-Methoxyphenyl)-1-piperazinyl]propyl]-3-methyl-4-oxo-2-phenyl-4H-1-benzopyran-8-carboxamide, also known as Recordati 15/2739 or SB 216469.



REC 15/2739

REC 15/2739 is an alpha 1-a adrenergic receptor antagonist
 5 and can be prepared according to the procedures described in U.S. Patent No. 5,403,842 which issued on April 4, 1995.

A131701 is (3aR-cis)-3-[2-(1,3,3a,4,5,9b-hexahydro-6-methoxy-2H-benz[e]isoindol-2-yl)ethyl]-pyrido[2',3':4,5]thieno[3,2-d]pyrimidine-2,4(1H,3H)-dione.

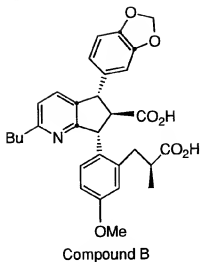


A131701

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A131701 is an alpha 1-a adrenergic receptor antagonist and
 can be prepared according to the procedures outlined in U.S. Patent No. 5,597,823 which issued on January 28, 1997.

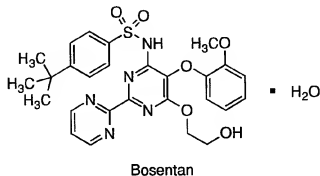
A number of endothelin antagonists have been disclosed as
 15 useful for inhibiting vasoconstriction. This antagonism can be helpful in alleviating the symptoms of BPH. These endothelin antagonists and their utility as inhibitors of vasoconstriction are described in U.S. Patent No. 5,389,629, which issued on February 14, 1995. More particularly, BQ-4508-2 disclosed in U.S. Patent No. 5,389,620, and referred to herein as
 20 "Compound B," is a potent, subtype non-selective endothelin antagonist.



Compound B can be prepared according to the procedures described in U.S. Patent No. 5,389,620 or according to the process disclosed herein.

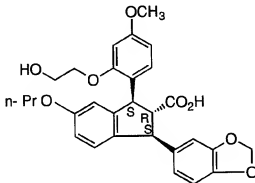
Compound B and the pharmaceutically acceptable salts thereof inhibit endothelin, which induces sustained contraction of either vascular or non-vascular smooth muscle. By inhibiting endothelin, Compound B can effect a relaxation of smooth muscle tissue and prove helpful in treating BPH.

Bosentan is *p-tert-Butyl-N-[6-(2-hydroxyethoxy)-5-(o-methoxyphenoxy)-2-(2-pyrimidinyl)-4-pyrimidinyl]benzenesulfonamide monohydrate*, also known as Ro-47-0203/029.



Bosentan is an endothelin antagonist and can be prepared according to the procedures described in U.S. Patent No. 5,292,740 which issued March 8, 1994.

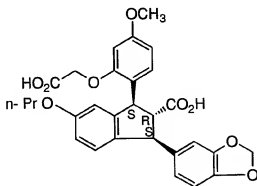
- SB217242 is [1S-(1.alpha.,2.beta.,3.alpha.)]-1-(1,3-benzodioxol-5-yl)-2,3-dihydro-3-[2-(2-hydroxyethoxy)-4-methoxyphenyl]-5-propoxy-1H-Indene-2-carboxylic acid.



SB217242

- SB217242 is an endothelin antagonist and can prepared according to the procedures described in WO 94/25013 which published on November 10, 1994.

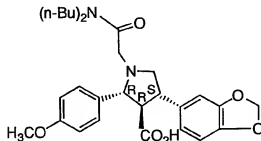
- SB209670 is [1S-(1.alpha.,2.beta.,3.alpha.)]-1-(1,3-benzodioxol-5-yl)-3-[2-(carbomethoxy)-4-methoxyphenyl]-2,3-dihydro-5-propoxy-1H-Indene-2-carboxylic acid.



SB209670

SB209670 is an endothelin antagonist and can be prepared according to the procedures described in WO 94/25013 which published on November 10, 1994.

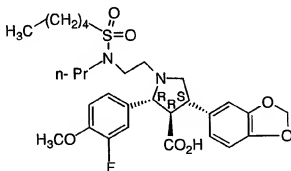
- 5 A 127722 is (2.alpha.,3.beta.,4.alpha.)-4-(1,3-Benzodioxol-5-yl)-1-[2-(dibutylamino)-2-oxoethyl]-2-(4-methoxyphenyl)-3-pyrrolidinecarboxylic acid.



A 127722

- 10 A 127722 is an endothelin antagonist and can be prepared according to the procedures outlined in WO 96/06095 which published on February 29, 1996.

- 15 A 182086 is [2R-(2.alpha.,3.beta.,4.alpha.)]-4-(1,3-Benzodioxol-5-yl)-2-(3-fluoro-4-methoxyphenyl)-1-[2-[(pentylsulfonyl)propylamino]ethyl]-3-pyrrolidinecarboxylic acid.



A 182086

A 182086 is an endothelin antagonist and can be prepared according to the procedures outlined in WO 97/30045 which published on August 21, 1997.

For the utility employed herein, the end product compounds of the present invention may be administered orally, parenterally (including subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques), by inhalation spray, or rectally, in dosage unit formulations containing conventional non-toxic pharmaceutically-acceptable carriers, adjuvants and vehicles.

These pharmaceutical compositions may be in the form of orally-administrable suspensions or tablets; nasal sprays; sterile injectable preparations, for example, as sterile injectable aqueous or oleaginous suspensions or suppositories.

In accordance with the method of the present invention, the individual components of the combination can be administered separately at different times during the course of therapy or concurrently in divided or single combination forms. For example, in a two-component combination including Compound A and Compound B, treatment with Compound B can commence prior to, subsequent to or concurrent with commencement of treatment with Compound A. The instant invention is therefore to be understood as embracing all such regimes of simultaneous or alternating treatment and the term "administering" is to be interpreted accordingly.

When administered orally as a suspension, these compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may contain microcrystalline cellulose for imparting bulk, alginic acid or sodium alginate as a suspending agent, methylcellulose as a viscosity enhancer, and sweeteners/flavoring agents known in the art. As immediate release tablets, these compositions may contain microcrystalline cellulose, dicalcium phosphate, starch, magnesium stearate and lactose and/or other excipients, binders, extenders, disintegrants, diluents and lubricants known in the art.

When administered by nasal aerosol or inhalation, these compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives,

absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art.

The injectable solutions or suspensions may be formulated according to known art, using suitable non-toxic, parenterally-acceptable diluents or solvents, such as mannitol, 1,3-butanediol, water, Ringer's solution or isotonic sodium chloride solution, or suitable dispersing or wetting and suspending agents, such as sterile, bland, fixed oils, including synthetic mono- or diglycerides, and fatty acids, including oleic acid.

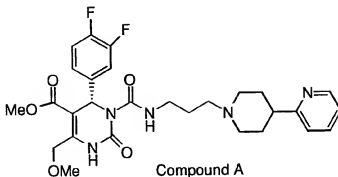
When rectally administered in the form of suppositories, these compositions may be prepared by mixing the drug with a suitable non-irritating excipient, such as cocoa butter, synthetic glyceride esters or polyethylene glycols, which are solid at ordinary temperatures, but liquify and/or dissolve in the rectal cavity to release the drug.

The alpha-1a antagonists may be employed in the present invention over a dosage range of from about 0.01 mg per subject to about 500 mg per subject. More particularly the effective amount of alpha-1a compound is about 0.1 mg to about 60 mg and in a subclass 1 mg to about 20 mg. One exemplification of this subclass ranges from 5 mg to about 20 mg with specific example of 10, 12.5 and 15 mg.

The endothelin antagonists may be employed in the instant invention over a dosage range of from about 0.1 to 750 mg. More particularly the dosage will vary from about 0.1 to about 100 mg and for the more potent compounds from 0.1 to about 2 mg.

Optionally the composition or method of the instant invention, employs a 5 alpha reductase inhibitor e.g., finasteride. A suitable dosage range for this 5 alpha reductase inhibitor is 1 mg to 10 mg exemplified by 5 mg. It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

The term "Compound A," as used herein refers to the free base shown below:



Compound A and its utility for antagonizing the alpha-1a adrenergic receptor, for treating BPH and for inhibiting lower urinary tract tissue is described in detail in WO 96/14846. Compound A is readily prepared according to the procedure of Example 30 in WO 96/14846.

The term "selective alpha-1a adrenergic receptor antagonist," as used herein, refers to an alpha-1a antagonist compound which is at least ten fold selective for the human alpha-1a adrenergic receptor as compared to the human alpha 1b, alpha 1d, alpha 2a, alpha 2b and alpha 2c adrenergic receptors. Methods of identification of selective alpha-1a receptor antagonists are disclosed in U.S. Patent No. 5,403,847 which issued on April 4, 1995.

The term "lower urinary tract tissue," as used herein, refers to and includes, but is not limited to, prostatic smooth muscle, the prostatic capsule, the urethra and the bladder neck.

The term "improving lower urinary tract symptoms" as used herein includes increasing urine flow rate, decreasing residual urine volume and improving overall obstructive and irritative symptoms in patients with benign prostatic hyperplasia or symptomatic prostatism.

The term "subject," as used herein refers to an animal, preferably a mammal, most preferably a human, who has been the object of treatment, observation or experiment.

The term "therapeutically effective amount" as used herein means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes alleviation of the symptoms of the disease being treated. Since the instant invention refers to compositions comprising two or more agents, the "therapeutically effective amount" is that amount of the combination of the agents taken together so that the combined effect elicits the desired biological or medicinal response. For example, the therapeutically effective amount of a composition comprising Compound A and Compound B would be the amount of Compound A and the amount of Compound B that when taken together have a combined effect that is therapeutically effective.

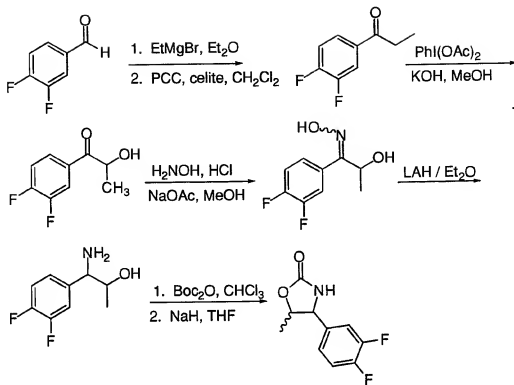
As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

Abbreviations used in the instant specification, particularly the Schemes and Examples, are as follows:

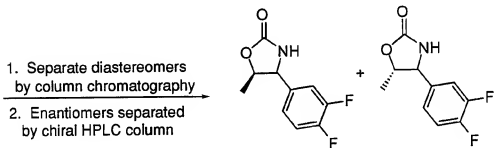
Ac = acetyl
DMF = N,N-dimethylformamide
EDC = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
EtOAc = ethyl acetate
HOAt = 1-hydroxy-7-azabenzotriazole
Me = methyl
MeOH = methanol
THF = tetrahydrofuran

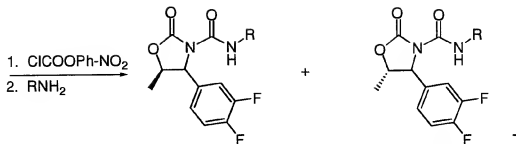
Scheme 1 and Example 1 pertain to the preparation of Compound C.

Scheme 1



Scheme 1, continued





Only two of the possible four structures shown.

Absolute stereochemistry was not established

The following examples are provided to further define the invention without, however, limiting the invention to the particulars of these examples.

EXAMPLE 1

Preparation of *trans* (+)-4-(3,4-Difluorophenyl)-5-methyl-2-oxo-oxazolidine-3-carboxylic acid(3-[4-(4-fluorophenyl)-piperidin-1-yl]propyl)amide

a. 1-(3,4-Difluorophenyl)propan-1-ol

To a solution of 3,4-difluorobenzaldehyde (5.0 g, 35.2 mmol) in diethyl ether (35 mL) in a round bottom flask was added a solution of ethylmagnesium bromide in THF (38.0 mL, 38.0 mmol) at 0° C. The reaction mixture was stirred at 0° C for 1 h when TLC analysis indicated that the reaction was complete ($R_f = 0.5$, 8:1 hexane/EtOAc). The reaction was quenched carefully by adding 38 mL of water. It was extracted with diethyl ether (2 X 30 mL), washed with brine and the organic layer was dried over Na_2SO_4 . The solvent was removed in vacuo after filtration and 1-(3,4-difluorophenyl)propan-1-ol was obtained as a yellow oil (crude wt. = 6.0 g) which looked > 90% pure by NMR. It was used in the next step without purification.

b. 1-(3,4-Difluorophenyl)propan-1-one

In a round bottom flask containing pyridinium chlorochromate (12.5 g, 58.1 mmol) was added celite 545 (25 g) and with the help of a magnetic

stirrer the solids were mixed together. 200 mL of CH_2Cl_2 was added followed by a solution of 1-(3,4-difluorophenyl)propan-1-ol (5.0 g, 29.1 mmol) in 10 mL of CH_2Cl_2 and the resulting brown suspension was stirred overnight at room temperature. The suspension was filtered through a sintered glass funnel and the solvent was removed in vacuo from the pale green colored filtrate. The green oil was then diluted with diethyl ether (200 mL) and it was filtered through a pad of celite to remove the metal impurities. The solvent was removed in vacuo to obtain 1-(3,4-difluorophenyl)propan-1-one as a pale yellow oil (3.4 g, 69% yield). It was used in the next step without purification.

c. 1-(3,4-Difluorophenyl)-2-hydroxy-propan-1-one
In a round bottom flask containing 200 mL of MeOH was added pellets of potassium hydroxide (23.0 g, 410.0 mmol). The solution was cooled to 0°C and 1-(3,4-difluorophenyl)-2-hydroxy-propan-1-one (7.0 g, 41.2 mmol) in 10 mL MeOH was added dropwise. The solution was stirred for 10 min and then iodobenzene diacetate (22.5 g, 70 mmol) was added in two portions. The solution first became orange and then turned yellow. It was stirred overnight at room temperature and then the solvent was removed in vacuo. The residue was dissolved in water and was extracted with ethyl acetate (3 X 100 mL). The combined organic extracts were washed with brine and then dried over Na_2SO_4 . After filtration, the solvent was removed in vacuo to get 1-(3,4-difluorophenyl)-2-hydroxy-propan-1-one dimethyl acetyl as a yellow viscous oil (crude wt. = 9.2 g). It was dissolved in 150 mL of acetone and 10 drops of concentrated sulfuric acid were added. After stirring for 3 h, TLC analysis indicated that the reaction was complete. Acetone was removed in vacuo and after basification with saturated NaHCO_3 , the residue was extracted in EtOAc and was washed with brine. The organic layer was separated, dried over Na_2SO_4 and then filtered. The solvent was removed in vacuo and the residue was purified by silica gel chromatography (R_f = 0.4, 3:2 hexane/EtOAc) to obtain 1-(3,4-difluorophenyl)-2-hydroxy-propan-1-one as a pale yellow oil (3.3 g, 51% yield over two steps).

d. 1-(3,4-Difluorophenyl)-2-hydroxy-propan-1-one-oxime

- To a well stirred solution of 1-(3,4-difluorophenyl)-2-hydroxy-propan-1-one (5.5 g, 29.6 mmol) in MeOH (200mL) was added hydroxylamine hydrochloride (2.6 g, 38.4 mmol) and sodium acetate (8.1 g, 59.2 mmol) and the turbid solution was stirred overnight at room temperature. The solvent was evaporated and the residue was extracted with CH_2Cl_2 . The organic layer was washed with sat. NaHCO_3 , separated, dried over Na_2SO_4 and then filtered. The solvent was removed in vacuo to obtain 1-(3,4-Difluorophenyl)-2-hydroxy-propan-1-one-oxime as an orangish yellow oil (5.3 g, 97%). It was used in the next step without purification.
- 10 e. 1-Amino-1-(3,4-difluorophenyl)-propan-2-ol
- To a well stirred solution of 1-(3,4-difluorophenyl)-2-hydroxy-propan-1-one-oxime (5.8 g, 28.4 mmol), was added a 1.0 M solution of LiAlH_4 in ether (90 mL, 90 mmol) dropwise at 0°C . The resulting yellow solution was then stirred at room temperature for 2 h. The reaction mixture was cooled to 0°C and then carefully quenched sequentially with 3.5 mL of water, 3.5 mL of 3N NaOH followed by 10.5 mL of water. The resulting suspension was filtered thru a fritted glass funnel. To the residue was added 100 mL Et_2O and the suspension was heated to reflux for 20 min.
- 15 20 The suspension was filtered and was combined with the previous filtrate, dried over MgSO_4 , filtered and the solvent was removed in vacuo. 1-Amino-1-(3,4-difluorophenyl)-propan-2-ol was obtained as a yellow glassy syrup (3.6 g, 66%) which was used in the next step without further purification.
- 25 f. [1-(3,4-Difluorophenyl)-2-hydroxy-propyl]-carbamic acid-tert-butyl ester
- To a solution of 1-amino-1-(3,4-difluorophenyl)-propan-2-ol (3.5 g, 19.1 mmol) in CHCl_3 (15 mL) at 0°C was added a solution of di-tert-butyl dicarbonate (5.1 g, 23.6 mmol) in CHCl_3 (10 mL) in one portion and the resulting solution was stirred overnight at room temperature. The solvent was removed in vacuo and the residue was subjected to column chromatography on silica gel (2:1 hexane-EtOAc followed by EtOAc) to obtain [1-(3,4-difluorophenyl)-2-hydroxy-propyl]-carbamic acid-tert-butyl ester as a viscous oil (3.3 g, 60.2%).
- 30 35

g. 4-(3,4-Difluorophenyl)-5-methyl-oxazolidin-2-one

To a well stirred solution of [1-(3,4-difluorophenyl)-2hydroxy-propyl]-carbamic acid-tert-butyl ester (0.43 g, 1.5 mmol) THF (20 mL) was added 95% NaH (0.09 g, 3.8 mmol) at room temperature. The resulting suspension was stirred for 3 h at about 35°C (warm water bath) and then quenched carefully with ice. The biphasic mixture was extracted with 100 mL of EtOAc, washed with brine, dried over Na_2SO_4 , filtered and the solvent was removed in vacuo. The two diastereomers were separated by column chromatography over silica gel (First isomer: 0.11g, $R_f = 0.6$, 3:1 hexane-EtOAc; second isomer: 0.23 g, $R_f = 0.5$, 3:1 hexane-EtOAc). NOE experiment suggested that the first diastereomer had the methyl and the aryl group in *trans* configuration while the second diastereomer had *cis* relationship between the two groups.

Enantiomers of each of these diastereomers were separated by HPLC using Chiralcel OD (4.6 X 250 mm) using 80% hexane /20% isopropyl alcohol/ 0.1% diethylamine as the eluting system (12 mL/min) under isothermal conditions (U.V. 254 nm). The retention times for the two isomers of the *trans*-oxazolidinone were 12.1 min ($[\alpha]_D = +36.4$ ($c = 0.25$, acetone)) and 15.6 min ($[\alpha]_D = -30.8$ ($c = 0.20$, acetone)), respectively. The retention times for the two isomers of the *cis*-oxazolidinone were 13.7 min ($[\alpha]_D = +65.8$ ($c = 0.92$, acetone)) and 19.9 min ($[\alpha]_D = -65.8$ ($c = 0.74$, acetone)), respectively.

h. 4-(3,4-Difluorophenyl)-5-methyl-2-oxo-oxazolidine-3-carboxylic acid-4-nitro-phenyl ester

To a suspension of 95% NaH (0.01 g, 0.038 mmol) in 5.0 mL of anhydrous THF under argon, a solution of 4-(3,4-difluorophenyl)-5-methyl-oxazolidin-2-one (0.07 g, 0.33 mmol) in 5.0 mL THF was added dropwise via a syringe. The resulting suspension was stirred at room temperature for 20 min. This suspension was then added dropwise via a syringe into another round bottom flask containing a solution of 4-nitrophenylchloroformate (0.08 g, 0.4 mmol) in 10 mL of THF, cooled at -78°C, over a period of 15 min. The stirring was continued for 1 h after which the solvent was removed and the residue was purified by column

chromatography on silica gel with 1:1 hexane/ CH_2Cl_2 followed by CH_2Cl_2 ($R_f = 0.4$, CH_2Cl_2) to obtain 4-(3,4-difluorophenyl)-5-methyl-2-oxo-oxazolidine-3-carboxylic acid-4-nitro-phenyl ester as a white solid (0.07 g, 56%).

5

i. 3-[4-(4-Fluoro-phenyl)-piperidin-1-yl]-propylamine

To a solution of 4-fluorophenylmagnesium bromide (110.0 mmol, 55.0 mL of 2.0 M solution) in 150.0 mL THF at 0°C was added 1-benzyl-4-piperidone (55.0 mmol, 10.2 mL) dropwise. The resulting solution was stirred under argon atmosphere for 1.5 h and then quenched with 100.0 mL of saturated NH_4Cl solution. The organic layer was separated and the aqueous layer was extracted with 100.0 mL of Et_2O . The combined organic extracts were washed with brine, separated and dried over Na_2SO_4 . The solution was filtered and the solvent was removed in vacuo to obtain a yellow oil which was purified by passing through a silica gel column with 4:1 hexane/ EtOAc followed by 1:1 hexane/ EtOAc as the eluting system. 1-Benzyl-4-(4-fluoro-phenyl)-piperidin-4-ol was obtained as a pale yellow oil in 89% yield (13.9 g). It was dissolved in 150.0 mL of toluene and p-toluenesulfonic acid monohydrate (50.0 mmol, 9.5 g) was added. The organic extracts were combined, washed with brine and the organic layer was dried over Na_2SO_4 . The solvent was removed in vacuo to obtain 1-benzyl-4-(fluoro-phenyl)-1,2,3,6-tetrahydro-pyridine as a yellow viscous oil (12.0 g, 92% yield) which was used in the next step without further purification.

25

To a solution of 1-benzyl-4-(fluoro-phenyl)-1,2,3,6-tetrahydro-pyridine (45.0 mmol, 12.0 g) in 100 mL MeOH was added 1.0 g of $\text{Pd}(\text{OH})_2$ and the resulting suspension was hydrogenated under 200 psi of H_2 in a stainless steel bomb for two days. The suspension was passed through a pad of celite and the filtrate was concentrated in vacuo to obtain 4-(4-fluoro)-phenyl-piperidine (6.5 g, 94%) as a viscous oil. It was converted into 3-[4-(4-fluoro-phenyl)-piperidin-1-yl]-propylamine.

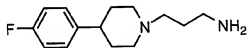
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j. *trans* (+)-4-(3,4-Difluorophenyl)-5-methyl-2-oxo-oxazolidine-3-carboxylic acid[3-[4-(4-fluorophenyl)-piperidin-1-yl]propyl]amide

- To a solution of 3-amino-propyl-4-(4-fluoro)phenyl-piperidine (0.04 g, 0.12 mmol) in 10 mL of THF *trans* (+)-4-(3,4-difluorophenyl)-5-methyl-2-oxo-oxazolidine-3-carboxylic acid-4-nitro-phenyl ester (0.03g, 0.08 mmol) (made from the (+)-enantiomer from HPLC of the *trans* diastereomer separated by column chromatography) was added and the resulting yellow solution was stirred under argon atmosphere for 10 h at room temperature. The solvent was removed in vacuo and the residue was purified by column chromatography over silica gel with EtOAc followed by 15% MeOH in EtOAc as the eluting systems to obtain *trans* (+)-4-(3,4-difluorophenyl)-5-methyl-2-oxo-oxazolidine-3-carboxylic acid{3-[4-(4-fluorophenyl)-piperidin-1-yl]propyl}amide in 70% yield. It was converted into its hydrochloride salt.
- M.P. = 80-83°C (shrinks around 58°C); $[\alpha]_D = +27.4$ ($c = 0.49$, MeOH); Anal. Calcd. for $C_{28}H_{29}N_3O_3F_3Cl \cdot 1.0 H_2O$: C, 56.55; H 6.07; N 7.91 Found: C, 56.49; H, 5.88; N, 7.80.

EXAMPLE 2

3-[4-(4-Fluorophenyl)piperidin-1-yl]propylamine



20

Step A. 4-(4-Fluorophenyl)piperidine hydrochloride

- To a solution of 4-(4-fluorophenyl)-1,2,3,6-tetrahydropyridine hydrochloride (10 g) in methanol (200 mL) was added 10% palladium on charcoal (0.5 g) and the mixture was hydrogenated at 50 psi for 3 h. The catalyst was removed by filtration and solvent was evaporated to leave the product as a white powder, which was used in the next step without any purification. The 1H -NMR and TLC analysis showed this product to be pure. M.P. 181-182 °C.

- 1H NMR ($CDCl_3$): δ 1.95-2.03 (br d, 2H), 2.14-2.29 (m, 2H), 2.70-2.80 (m, 1H), 2.91-3.07 (br q, 2H), 3.60-3.64 (br d, 2H), 6.96-7.03 (m, 2H), 7.19-7.22 (m, 2H), 9.60 (br s, 1H), 9.71 (br s, 1H).

Step B. 3-[4-(4-Fluorophenyl)piperidin-1-yl] propylphthalimide

A mixture of 4-(4-fluorophenyl)piperidine hydrochloride (5.08 g, 23.2 mmol), 3-bromopropylphthalimide (6.22 g, 23.2 mmol), and potassium carbonate (15 g) in DMF (100 mL) was stirred and heated at 95-100 °C for 12 h. About 80% of the solvent was evaporated at reduced pressure, the residue was diluted with ethyl acetate (200 mL) and washed with brine (3 X 100 mL) and dried (Na₂SO₄). Solvent was evaporated and the residue was purified by column chromatography on silica gel using 1/1 hexane-ethyl acetate to 100% ethyl acetate as eluent. This product was crystallized from isopropanol to give a white crystalline solid; m.p. 80-81 °C. This material was used in the next step. Concentration of the mother liquor and cooling gave the second crop.

¹H NMR (CDCl₃): δ 1.43-1.52 (m, 2H), 1.67-1.75 (m, 2H), 1.80-1.96 (m, 4H), 2.33-2.46 (m, 3H), 2.94-2.99 (br d, 2H), 3.78 (t, *J* = 7 Hz, 2H), 6.90-7.04 (m, 4H), 7.70-7.74 (m, 2H), 7.84-7.87 (m, 2H).

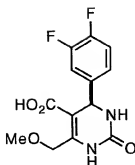
Step C. 3-[4-(4-Fluorophenyl)piperidin-1-yl]propylamine

To a solution of 3-[4-(4-fluorophenyl)piperidin-1-yl]propylphthalimide (4.5 g, 12.3 mmol) in methanol (200 mL), hydrazine (4 mL) was added and the mixture was stirred and refluxed for 8 h. It was cooled, and the white solid was filtered and washed with methanol (20 mL). Solvent was evaporated, and the residue was dried under vacuum for 4 h. Chloroform (50 mL) was added to this material, it was stirred for 1 h and filtered. The white solid was washed with more chloroform (20 mL), and the solvent was evaporated from the combined filtrates to leave the crude product as an oil. It was purified by column chromatography on silica gel using dichloromethane/methanol/2M ammonia in methanol (10/3/1) as the eluent.

¹H NMR (CDCl₃): δ 1.60-1.83 (m, 6H), 1.96-2.07 (m, 4H), 2.40-2.55 (m, 3H), 2.70-2.85 (br t, 2H), 3.03-3.07 (br d, 2H), 6.93-7.00 (m, 2H), 7.14-7.20 (m, 2H).

EXAMPLE 3

(-)-4-Methoxymethyl-1,2,3,6-tetrahydro-2-oxo-6-(3,4-difluorophenyl)-pyrimidine-5-carboxylic acid



To a well stirred mixture of methyl-4-methoxyacetoacetate (50 g, 0.351 mol), 3,4-difluorobenzaldehyde (51.39 g, 0.351 mmol), and urea (31.64 g, 0.527 mole) in THF (300 mL) at room temperature were added sequentially copper(I) oxide (5.06 g, 0.035 mole) and acetic acid (2.05 mL) followed by the dropwise addition of boron trifluoride diethyl etherate (56 mL, 0.456 mole). The mixture was stirred and refluxed for 8 h, whereupon TLC indicated completion of the reaction. It was cooled and poured into a mixture of ice and sodium bicarbonate (100 g). The resulting mixture was filtered through celite. The celite was washed with dichloromethane (400 mL). The organic layer was separated and the aqueous layer was extracted with dichloromethane (3 X 300 mL). The combined organic extracts were dried (sodium sulfate) and the solvent was evaporated. The crude product was purified by flash column chromatography on silica gel using 50% ethyl acetate in hexanes and then ethyl acetate as eluent to give the product as a pale yellow foam.

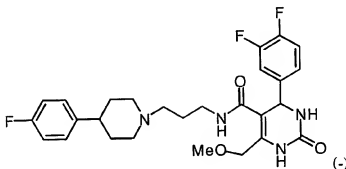
¹H NMR (CDCl₃) δ 3.476 (s, 3H), 3.651 (s, 3H), 4.653 (s, 2H), 5.39 (s, 1H), 6.60 (br s, 1H, NH), 7.00-7.20 (m, 3H), 7.72 (br s, 1H, NH).

The racemic intermediate 5-methoxycarbonyl-4-methoxymethyl-1,2,3,6-tetrahydro-2-oxo-6-(3,4-difluorophenyl)-pyrimidine was resolved by chiral HPLC [Chiralcel OD 20 X 250 mm #369-703-30604; 1254 nm; hexanes/ethanol 90/10; 85 mg per injection; the 2nd enantiomer peak to elute] to give (-)-5-methoxycarbonyl-4-methoxymethyl-1,2,3,6-tetrahydro-2-oxo-6-(3,4-difluorophenyl)-pyrimidine.

The material is hydrolyzed to the acid by standard means using sodium or lithium hydroxide in methanol.

EXAMPLE 4

(-)-4-(3,4-Difluorophenyl)-6-methoxymethyl-2-oxo-1,2,3,4-tetrahydro-
pyrimidine-5-carboxylic acid [3-[4-(4-fluorophenyl)-piperidin-1-yl]-
propyl]-amide



To a suspension of 2.5 g (8.3 mmol) DHP acid prepared in accordance with the procedure of Example 3 and 2.0g (8.5 mmol) amine prepared in accordance with the procedure of Example 2 in 20 ml DMF was added 1.18 (8.7 mmol) HOAt and 1.65g (8.6 mmol) EDC. The suspension was stirred 2 h at room temperature, then poured into 700 ml EtOAc and washed with 250 ml saturated aqueous sodium bicarbonate, 300 ml dilute brine, and brine. The organic layer was dried over Na₂SO₄, filtered, and concentrated. Purification by flash chromatography (7.5 x 16 cm silica gel, linear gradient 5-10% MeOH / 1%NH₄OH / CH₂Cl₂) followed by crystallization from 150 ml of 2:1 EtOAc/hexanes gave the pure title compound. mp 149-150 °C.

¹H NMR (400 MHz, CDCl₃) δ 7.38 (s, 1H); 7.20-7.04 (m, 5H); 6.99 (t, 2H, *J* = 8.69 Hz); 6.86 (br t, 1H, *J* = 4.84 Hz); 5.82 (s, 1H); 5.41 (d, 1H, *J* = 2.47 Hz); 4.49 (d, 1H, *J* = 14 Hz); 4.31 (d, 1H, *J* = 14 Hz); 3.42 (s, 3H); 3.37 (m, 1H); 3.21 (m, 1H); 2.93 (d, 1H, *J* = 11.3 Hz); 2.82 (d, 1H, *J* = 11.8 Hz); 2.46 (tt, 1H, *J* = 12.2 and 3.75 Hz); 2.31 (m, 2H); 1.95 (m, 2H); 1.79 (m, 2H); 1.66-1.47 (M, 4H).

HRMS (M+H calc 517.2421 found 517.2402). [α]_D²³ -76° (c=0.84 CH₂Cl₂).

Analysis:

Calcd. for C₂₇H₃₁F₃N₄O₃•0.25 H₂O

C, 62.23; H, 6.09; N, 10.75
Found: C, 62.17, H, 6.07; N, 10.89

EXAMPLE 5

5

Methodology for determining the efficacy of ET antagonists and Alpha-1a antagonists for inhibition of ET-1 and alpha 1 receptor mediated prostatic urethral contractions in a mongrel dog model

10 Methods:

Male mongrel dogs are fasted overnight the anesthetized with Sodium Pentobarbital at 35 mg/kg, iv to effect, followed by a 4 mg/kg/hr iv infusion. A cuffed endotracheal tube is inserted and each animal ventilated with room air using a positive displacement large animal ventilator at a rate of 18 breaths/minute and an average tidal volume of 18 ml/kg body weight. Body temperature is maintained with a heating pad and a temperature controller connected to an esophageal temperature probe. Two catheters are placed in the aorta via the femoral arteries (one in each artery) for administration of endothelin or phenylephrine and for continuous direct monitoring of blood pressure and heart rate using a pressure transducer and a computer-based data acquisition system (Modular Instruments, Inc.). Two additional catheters were placed in the vena cava via the femoral veins (one in each vein) for administration of pentobarbital or either the endothelin antagonist or the alpha 1a receptor antagonist. A supra-pubic incision is made approximately one-half inch lateral to the penis and the ureters, urinary bladder, prostate and urethra are exposed. The dome of the bladder is retracted to facilitate dissection of the ureters. The ureters are cannulated and then ligated, permitting urine to flow freely without filling the bladder. Umbilical tape is passed beneath the bladder neck and 1-2 cm distal to the prostate. The bladder dome is incised and a Millar microtip catheter transducer is advanced into the urethra. The neck of the bladder is ligated with the umbilical tape to hold the transducer. The incision in the bladder dome is sutured with 3-0 silk.

35 The transducer is withdrawn until the tip is in located in the prostatic

urethra. The position of the catheter is verified by gently squeezing the prostate and noting the large increase in prostatic urethral pressure. The distal ligature is then tied.

5 Protocol:

Phenylephrine (10 ug/kg, ia) is administered and the pressor effect on intraurethral pressure (IUP) is measured. When blood pressure and IUP return to baseline, endothelin-1 (ET-1, 1 nmole/kg, ia) is administered and the increase in IUP is measured. When the blood
10 pressure and IUP return to baseline (1 hour later), an efficacious dose of and endothelin antagonist or alpha-1a antagonist is administered. Ten to fifteen minutes later (when blood pressure has stabilized) the pressor responses to phenylephrine and ET-1 are measured again.

15 Results:

The results of the experiment will demonstrate that the endothelin antagonist will completely inhibit the IUP pressor response to ET-1 but not phenylephrine. The alpha-1a antagonist will inhibit the IUP pressor response to phenylephrine, but not to ET-1.

20

Conclusion:

The conclusion is that both ET-1 and phenylephrine can increase prostatic urethral tone independently and can be inhibited by an endothelin antagonist and alpha 1a antagonist, respectively. Therefore, if
25 both ET-1 and alpha 1 adrenergic tone participate in prostatic urethral constriction in man (contributing to bladder outlet obstruction), then a combination therapy of an endothelin antagonist and alpha 1a antagonist will be more efficacious than either antagonist alone.

30

While the foregoing specification teaches the principles of the present invention, with examples provided for the purpose of illustration, it will be understood that the practice of the invention encompasses all of the usual variations, adaptations, modifications,

deletions or additions of procedures and protocols described herein, as come within the scope of the following claims and its equivalents.

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WHAT IS CLAIMED IS:

1. A composition comprising an alpha-1a adrenergic receptor antagonist and an endothelin antagonist, or pharmaceutically acceptable salts thereof.
2. The composition of Claim 1, wherein the alpha-1a adrenergic receptor antagonist is a selective alpha-1a adrenergic receptor antagonist.
3. The composition of Claim 2, wherein the selective alpha-1a adrenergic receptor antagonist is selected from Compound A, Compound C, Compound D, Compound E, KMD-3213, tamsulosin, REC 15/2739, A131701, or pharmaceutically acceptable salts thereof.
4. The composition of Claim 3, wherein the selective alpha-1a adrenergic receptor antagonist is Compound A or a pharmaceutically acceptable salt thereof.
5. The composition of Claim 3, wherein the selective alpha-1a adrenergic receptor antagonist is Compound D or a pharmaceutically acceptable salt thereof.
6. The composition of Claim 3, wherein the selective alpha-1a adrenergic receptor antagonist is Compound E or a pharmaceutically acceptable salt thereof.
7. The composition of Claim 1, wherein the endothelin antagonist is a subtype non-selective endothelin antagonist.
8. The composition of Claim 7, wherein the subtype non-selective endothelin antagonist is selected from Compound B, bosentan, SB217242, SB209670, A 127722, A 182086, or pharmaceutically acceptable salts thereof.

9. The composition of Claim 7, wherein the subtype non-selective endothelin antagonist is Compound B or a pharmaceutically acceptable salt thereof.
- 5 10. The composition of Claim 2, wherein the selective alpha-1a adrenergic receptor antagonist is Compound A and the endothelin antagonist is Compound B, or pharmaceutically acceptable salts thereof.
- 10 11. The composition of Claim 1, further comprising a 5a-reductase inhibitor.
12. A method of treating benign prostatic hyperplasia in a subject in need thereof which comprises administering to the subject
15 an effective amount of an alpha-1a antagonist, an endothelin antagonist, and optionally a 5a-reductase inhibitor.
13. The method of Claim 12, wherein the alpha-1a adrenergic receptor antagonist is selected from Compound A,
20 Compound C, Compound D, Compound E, KMD-3213, tamsulosin, REC 15/2739, or A131701 and the endothelin antagonist is selected from Compound B, bosentan, SB217242, SB209670, A 127722 or A 182086; or pharmaceutically acceptable salts thereof.
- 25 14. The method of Claim 13, wherein the alpha-1a adrenergic receptor antagonist is Compound A or a pharmaceutically acceptable salt thereof and the endothelin antagonist is Compound B or a pharmaceutically acceptable salt thereof.
- 30 15. The method of Claim 13, wherein the alpha-1a adrenergic receptor antagonist is Compound D or a pharmaceutically acceptable salt thereof and the endothelin antagonist is Compound B or a pharmaceutically acceptable salt thereof.

16. The method of Claim 13, wherein the alpha-1a adrenergic receptor antagonist is Compound E or a pharmaceutically acceptable salt thereof and the endothelin antagonist is Compound B or a pharmaceutically acceptable salt thereof.
17. A method of relaxing lower urinary tract tissue in a subject in need thereof which comprises administering to the subject an effective amount of an alpha-1a antagonist, an endothelin antagonist, and optionally a 5a-reductase inhibitor.
18. The method of Claim 17, wherein the alpha-1a adrenergic receptor antagonist is selected from Compound A, Compound C, Compound D, Compound E, KMD-3213, tamsulosin, REC 15/2739 or A131701 and the endothelin antagonist is selected from Compound B, bosentan, SB217242, SB209670, A 127722 or A 182086; or pharmaceutically acceptable salts thereof.
19. The method of Claim 18, wherein the alpha-1a adrenergic receptor antagonist is Compound A or a pharmaceutically acceptable salt thereof and the endothelin antagonist is Compound B or a pharmaceutically acceptable salt thereof.
20. The method of Claim 18, wherein the alpha-1a adrenergic receptor antagonist is Compound D or a pharmaceutically acceptable salt thereof and the endothelin antagonist is Compound B or a pharmaceutically acceptable salt thereof.
21. The method of Claim 18, wherein the alpha-1a adrenergic receptor antagonist is Compound E or a pharmaceutically acceptable salt thereof and the endothelin antagonist is Compound B or a pharmaceutically acceptable salt thereof.
22. A method of improving lower urinary tract symptoms in a benign prostatic hyperplasia patient which comprises administering to the subject an effective amount of an alpha-1a

antagonist, an endothelin antagonist, and optionally a 5a-reductase inhibitor.

23. The method of Claim 22, for increasing urine flow
5 rate.

24. The method of Claim 22, for decreasing residual
urine volume.

25. The method of Claim 22, wherein the alpha-1a
adrenergic receptor antagonist is selected from Compound A,
Compound C, Compound D, Compound E, KMD-3213, tamsulosin, REC
15/2739, or A131701 and the endothelin antagonist is selected from
Compound B, bosentan, SB217242, SB209670, A 127722 or A 182086; or
15 pharmaceutically acceptable salts thereof.

26. The method of Claim 25, wherein the alpha-1a
adrenergic receptor antagonist is Compound A or a pharmaceutically
acceptable salt thereof and the endothelin antagonist is Compound B or a
20 pharmaceutically acceptable salt thereof.

27. The method of Claim 25, wherein the alpha-1a
adrenergic receptor antagonist is Compound D or a pharmaceutically
acceptable salt thereof and the endothelin antagonist is Compound B or a
25 pharmaceutically acceptable salt thereof.

28. The method of Claim 25, wherein the alpha-1a
adrenergic receptor antagonist is Compound E or a pharmaceutically
acceptable salt thereof and the endothelin antagonist is Compound B or a
30 pharmaceutically acceptable salt thereof.

29. A pharmaceutical composition comprising an alpha-
1a adrenergic receptor antagonist and an endothelin antagonist, or
pharmaceutically acceptable salts thereof, and a pharmaceutically
35 acceptable carrier.

30. The pharmaceutical composition of Claim 29, comprising Compound A and Compound B, or pharmaceutically acceptable salts thereof, and a pharmaceutically acceptable carrier.
- 5
31. The pharmaceutical composition of Claim 29, comprising Compound D and Compound B, or pharmaceutically acceptable salts thereof, and a pharmaceutically acceptable carrier.
- 10
32. The pharmaceutical composition of Claim 29, comprising Compound E and Compound B, or pharmaceutically acceptable salts thereof, and a pharmaceutically acceptable carrier.
- 15
33. A pharmaceutical composition made by combining an alpha-1a antagonist, an endothelin antagonist, or pharmaceutically acceptable salts thereof, and a pharmaceutically acceptable carrier.
- 20
34. A process for making a pharmaceutical composition comprising combining an alpha-1a antagonist, an endothelin antagonist, or pharmaceutically acceptable salts thereof, and a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

Int. Application No

PCT/US 99/06014

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K45/06 A61K31/505 A61K31/435 //(A61K31/505,31:435)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 08487 A (MERCK & CO INC ;ASHTON WALLACE T (US); CHANG LINDA L (US); GREENLE) 21 March 1996 see page 80, line 19 - page 81, line 15; claims	1,7,12, 17,22, 29,33,34
Y	---	1-34
X	WO 96 04905 A (BROTEN THEODORE P ;KIECZYKOWSKI GERARD R (US); PETTIBONE DOUGLAS J) 22 February 1996 see page 94, line 19 - page 95, line 16 see page 1, line 13 - line 27	1,7,12, 22,29, 33,34
Y	---	1-34
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Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
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- "P" document published prior to the international filing date but later than the priority date claimed

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- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
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Date of the actual completion of the international search

25 June 1999

Date of mailing of the international search report

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/06014

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 617 001 A (MERCK & CO INC) 28 September 1994 see page 3, line 3 - line 14 see page 43, line 37 - line 55 ---	1,7,12, 22,29, 33,34
Y	---	1-34
X	WO 96 22978 A (RHONE-POULENC RORER LTD ;PORTER BARRY (GB); SMITH CHRISTOPHER (GB)) 1 August 1996 see page 22, line 31 - line 36 ---	1,7,12, 22,29, 33,34
Y	---	1-34
Y	WO 96 14846 A (SYNAPTIC PHARMA CORP ;NAGARATHNAM DHANAPALAN (US); CHIU GEORGE (US) 23 May 1996 cited in the application see page 34, line 17 - line 24; claims ---	1-34
Y	WO 96 22992 A (ABBOTT LAB) 1 August 1996 cited in the application see page 47, line 5 - line 9; claims ---	1-34
Y	EP 0 714 897 A (BANYU PHARMA CO LTD) 5 June 1996 cited in the application see page 23, line 21 - line 27 -----	1-34

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/06014

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9608487 A	21-03-1996	US 5559135 A AU 3629595 A	24-09-1996 29-03-1996
WO 9604905 A	22-02-1996	US 5565485 A AU 3276795 A CA 2195758 A EP 0774965 A JP 10503779 T US 5668176 A	15-10-1996 07-03-1996 22-02-1996 28-05-1997 07-04-1996 16-09-1997
EP 0617001 A	28-09-1994	AU 679710 B AU 5787894 A CA 2119051 A CN 1119434 A CZ 9502335 A FI 954404 A HR 940179 A HU 73658 A JP 8508034 T NO 953672 A NZ 263414 A PL 310661 A SK 114795 A WO 9421590 A US 5565485 A US 5767310 A US 5668176 A ZA 9401923 A	10-07-1997 22-09-1994 20-09-1994 27-03-1996 17-01-1996 18-09-1995 28-02-1998 30-09-1996 27-08-1996 17-11-1995 22-09-1997 27-12-1995 05-06-1996 29-09-1994 15-10-1996 16-06-1998 16-09-1997 14-10-1994
WO 9622978 A	01-08-1996	AU 4454196 A BR 9606961 A CA 2211646 A CZ 9702236 A EA 61 B EP 0805802 A FI 973111 A JP 10513158 T NO 973441 A NZ 298853 A PL 321545 A	14-08-1996 04-11-1997 01-08-1996 17-12-1997 30-04-1998 12-11-1997 25-09-1997 15-12-1998 15-09-1997 28-07-1998 08-12-1997
WO 9614846 A	23-05-1996	AU 4239896 A BG 101607 A BR 9509700 A CA 2205384 A CN 1173132 A CZ 9701512 A EP 0790826 A FI 972087 A HU 77941 A JP 10510247 T NO 972236 A PL 320263 A SK 60097 A	06-06-1996 27-02-1998 03-11-1998 23-05-1996 11-02-1998 15-07-1998 27-08-1997 14-07-1997 28-12-1998 06-10-1998 01-07-1997 15-09-1997 14-01-1998
WO 9622992 A	01-08-1996	US 5597823 A AU 705283 B AU 4745796 A	28-01-1997 20-05-1999 14-08-1996

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/06014

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9622992 A		CA 2211212 A EP 0808318 A	01-08-1996 26-11-1997
EP 0714897 A	05-06-1996	AU 675870 B AU 7351194 A CA 2169737 A CN 1129448 A WO 9505374 A JP 2847969 B US 5389620 A US 5714479 A	20-02-1997 14-03-1995 23-02-1995 21-08-1996 23-02-1995 20-01-1999 14-02-1995 03-02-1998